

REMARKS

Re-examination and reconsideration of the subject matter identified in caption, pursuant to and consistent with 37 C.F.R. §1.116, and in light of the remarks which follow, are respectfully requested.

In the Official Action, claims 1-6 and 8-10 stand rejected under 35 U.S.C. §102(b) as anticipated by WO 97/32644 (WO '644). Claims 1, 2, 4-6 and 8-10 also stand rejected under §102(b) as anticipated by Reuter '259 (U.S. Patent No. 5,872,259). Applicant respectfully traverses these rejections for at least the following reasons.

The present invention as defined by claim 1, is directed to a process for purifying a desired impure substance through emulsion crystallization comprising the steps of:

- (a) forming an emulsion of organic liquid droplets in a continuous water phase, which emulsion contains the impure substance;
- (b) super-saturating the emulsion in the substance;
- (c) inducing crystallization of the substance, whereby crystallization takes place in the water phase;
- (d) isolating the crystals of the substance resulting from step (c) from the emulsion, yielding an emulsion filtrate;
- (e) dissolving additional impure substance in the emulsion filtrate; and
- (f) repeating steps (b)-(d) with the emulsion obtained from step (e).

As can be seen from the above, additional impure substance is dissolved in the emulsion-filtrate from which the impure substance was crystallized, and a further crystallization of the desired substance is induced, whereby crystallization takes place in the continuous water phase.

In marked contrast to Applicant's process, Reuter '259 describes a very different procedure. An emulsion (transport phase 4) in a crystallization vessel (container 5) is passed

through a filter 8 to remove any crystals formed in the transport phase 4, then passed through a heat exchanger 9 to increase the temperature of the transport phase 4 to that of the first phase 1 of crude starting material, and then through column 3 containing the material to be purified. After contact of transport phase 4 with the first phase 1 over a sufficient column length, transport phase 4 is pumped through filter 10 and heat exchanger 9a, to reduce the temperature of the transport phase back to its original temperature (see Reuter '259 at column 6, lines 25 to 32). Thus, the design of the apparatus in Reuter '259 ensures that emulsion 4 (corresponding to the second phase in claim 1) which passes through column 3 (which contains the first phase according to claim 1 of Reuter '259) and contacts phase 1 over a sufficient column length is always saturated both with the substance to be purified and the impurity. This is further underlined by the language in claim 1 of Reuter '259 that "an equilibrium of the activities of the remaining substances in the aggregate mixture is maintained between the first phase and the second phase." After cooling this saturated emulsion back to the original temperature in container 5, the emulsion is supersaturated both with the substance and the impurity at a constant and very moderate level due to the moderate differences between the temperature in the crystallization container 5 and that in column 3.

Thus, a person skilled in the art and without hindsight, would conclude from the cited prior art that before the very first crystallization is started in container 5, the emulsion is already supersaturated with the desired substance and the impurity at a constant level. It necessarily follows that only the substance which is crystallized out in the first step is reloaded in column 3. Accordingly, the position of the Examiner regarding WO 97/32644 and Reuter '259 is disputed. In other words, "Reloading" in Reuter '259 only occurs with regard to the substance that is crystallized out, not with regard to the impurities. A non-steady-state mode of operation which corresponds to the process disclosed and claimed in the present application is neither

described nor suggested in Reuter '259. Such a process is excluded by the design and operation of the technique described therein.

WO 97/32644 describes the same principles, the same apparatus and the same procedure as in Reuter '259 but processes thermodynamically stable microemulsions, instead of macroemulsions. This is also evident from the description of WO '644 (see page 2, paragraph 2 of WO '644) where it is stated that microemulsions are used in order to avoid the use of high shear equipment and the oiling-out of emulsions and undesired spontaneous crystallization from large droplets. The fact that additional "impure substance" is dissolved in step (e) of the presently claimed invention with the resulting steps (b)-(d) being repeated according to step (f) clearly separates the invention from the cited prior art.

Turning to the "Response to Arguments" set forth on pages 6-7 of the Office Action, Applicant submits the following with regard to step (e) of the process of claim 1, i.e., "dissolving additional impure substance". The Examiner states that "impurities in the aggregate mixture are continuously added". However, as will be discussed below, the terms "saturation" and "dissolution" in physical chemistry relate to the state or change of state of an ensemble of molecules, i.e., they describe a macroscopic phenomenon and not the state or change of state of a single molecule. Dissolution means that a net amount of molecules dissolves. In discussing methods of purification of compounds on a technical scale, dissolution implies that measurable amounts of compound dissolve. At saturation, an equilibrium exchange of molecules between the solid phase and the solution is taking place. In case of dissolution, adsorption to the surface and desorption from the surface of the solid take place at different rates resulting in a macroscopic, measurable net dissolution of material. As indicated above, the process described in Reuter '259 and WO '644 is, in fact, steady state. In the steady state, no net transfer of materials takes place.

With respect to the Examiner's comments regarding the saturation-equilibrium point, Applicant submits the following definitions:

- Dissolution refers to the actual, macroscopic dissolution of a substance in a solvent. At saturation, an exchange of molecules is still going on between the solid material and dissolved material. However, dissolution does not proceed further once saturation is reached. The number of molecules re-entering the solid state is then equal to that entering the dissolved state.
- The definition of saturation is that a macroscopic amount of substance dissolved cannot exceed a certain concentration. Although the kinetic exchange of molecules from and to the solution can take place, this occurs at equal rates.

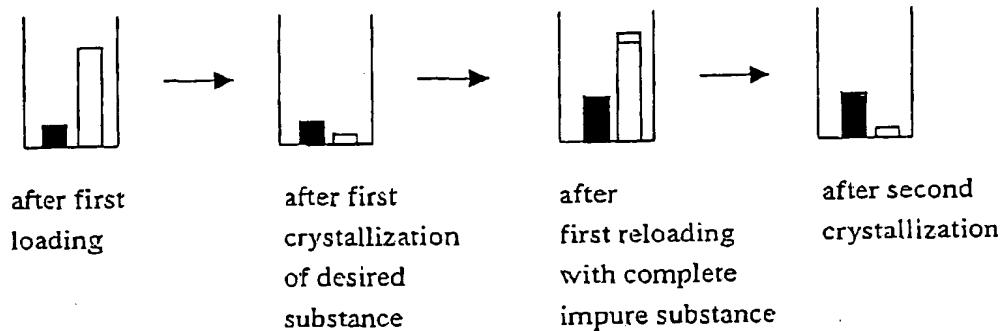
Thus, the definitions of saturation and dissolution relate to the macroscopic behavior of an ensemble of molecules, not to the fate of a single molecule.

Accordingly, Applicant disagree with the position of the Examiner that "if some impurities are absorbed (i.e. dissolved) along with the desired substance from the aggregate mixture, while other impurities from the previous cycle are released from the emulsion into waste stream 15, and there is no net accumulation of impurities into the emulsion", "that still meets applicants process steps as recited above because additional impure substance is dissolving in the emulsion filtrate during equilibrium, even though impurities are also released". It is not additional impure substance that is dissolved in Reuter '259 and WO '644 but molecules of the impurities being substituted by other molecules of the impurities. Complete "additional impure substance" as in element (e) of present claim 1 is not dissolved in the prior art process.

Thus, there is no additional dissolution of substance in the case of kinetic exchange in the steady state equilibrium and no additional "impure substance" (aggregate material) is added, only the component thereof that has crystallized out. In contrast, in the present

invention, the complete impure substance (aggregate mixture) is added. This distinction can be illustrated by the following schemes where the concentration of impurity in the crystallization container 5 is represented by a filled bar, that of the desired substance by open bars:

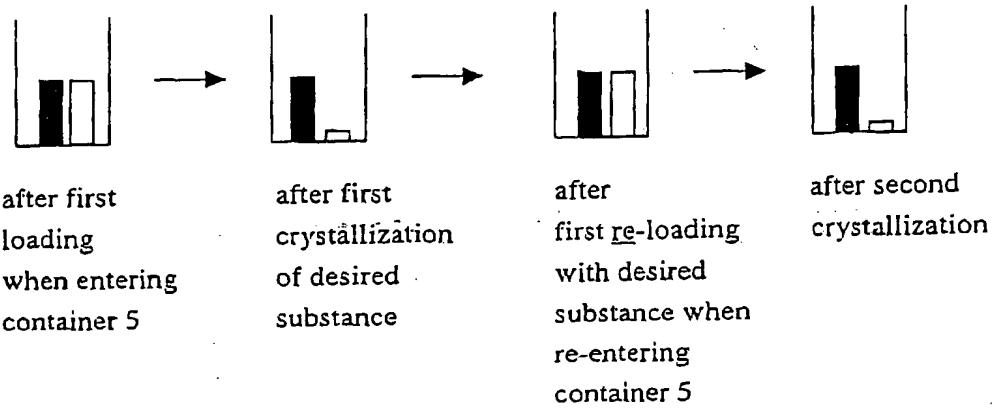
Scheme I: Present Invention



It can be seen that the concentration of the impurity increases at each stage.

In contrast, a comparable scheme for the cited prior art is shown in the following scheme:

Scheme II: Prior Art



As seen, the concentration of the impurity remains constant after each cycle.

In view of the above arguments, the differences between the presently claimed process and that of Reuter '259 and WO '644 are readily apparent. The conclusions drawn by the Examiner in the second paragraph on page 8 of the Office Action respectfully are considered to be erroneous for the following reasons:

- (1) the process in Reuter '259 and WO '644 is, in fact, a steady state operation rather than an unsteady state one;
- (2) an unsteady state operation is not possible in the process of Reuter '259 and WO '644 for reasons given above;
- (3) in the presently claimed process, the level of impurities builds up in the emulsion after each crystallization step due to the addition of further impure substance (i.e., impurities + desired substance) and only the desired substance is repeatedly removed.

For at least the foregoing reasons, Applicant respectfully submits that the present claims are novel and patentable over WO 97/32644 and Reuter (U.S. Patent No. 5,872,259). Withdrawal of the §102 rejections is respectfully requested.

Claims 1-10 stand rejected under 35 U.S.C. §103(a) as unpatentable over Reuter '259 in view of WO 97/32644 (WO '644) and Marsh (U.S. Patent No. 3,141,743). Claims 1-10 stand further rejected as unpatentable over WO 97/32644 (WO '644) in view of Marsh. Applicant respectfully traverses these rejections for at least the following reasons.

The deficiencies in the disclosures of Reuter '259 and WO '644 have been fully set forth previously. Marsh '743 is relied upon in the §103(a) rejections solely for a disclosure of centrifuging while washing crystals. As such, Marsh '743 in combination with Reuter '259 and WO '644 fails to disclose or suggest the process described in claims 1-10.

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For at least the foregoing reasons, Applicant respectfully submits that the present claims are patentable over Reuter (U.S. Patent No. 5,872,259) and/or WO 97/32644 as combined with Marsh (U.S. Patent No. 3,141,743). Withdrawal of the §103 rejections is requested.

Further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

If any issues remain outstanding, or should the examiner have any questions concerning the foregoing amendments and remarks, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

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